UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
MARSHALL DIVISION

ERFINDERGEMEINSCHAFT UROPEP GBR, Plaintiff, vs. ELI LILLY AND COMPANY, Defendant.	Court File No.: 2:15-cv-01202-WCB **JURY TRIAL DEMANDED**

DEFENDANT ELI LILLY & COMPANY'S REPLY BRIEF IN SUPPORT OF ITS MOTION FOR JUDGMENT AS A MATTER OF LAW OR, IN THE ALTERNATIVE, A NEW TRIAL

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

Cases

Statutes and Rules

I. THE CLAIMED METHOD REQUIRES USE OF A SPECIFIC SUBSET OF PDE V INHIBITORS NEITHER DESCRIBED NOR ENABLED BY THE PATENT TEXT

The written description and enablement issues turn on a comparison of the claimed invention to the four corners of the patent's disclosure. Each comparison leads to a conclusion of invalidity as a matter of law: the patent simply does not describe or enable UroPep's claim to broad, functionally-described genus of compounds administered in effective amounts for prophylaxis or treatment of BPH.

UroPep asserts that its invention was the discovery that PDE V has a functional role in the prostate and PDE V inhibition thus will treat BPH (e.g., Tr. 170:13-24)—implying that the difficulty in identifying compounds needed to effectuate that treatment is irrelevant. (Resp. at 30 n.10) But this cannot be correct. The discovery of such a natural correlation or a law of nature is simply not patentable. *See Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371 (Fed. Cir. 2015), cert denied, 136 S. Ct. 2511 (2016). Only when embodied in a concrete method of treatment using identified therapeutic agents can a biological discovery pass into the realm of patent-eligible subject matter, and that requires an adequate written description and enabling disclosure of the compounds contemplated for such use.

In reality, claim 1 requires use of a specific subset of PDE V inhibitors that are: (1) not the excluded compounds; (2) "selective" (i.e., 20 times more potent for PDE V versus PDE I-IV); and (3) "effective" in treating BPH which, UroPep concedes, requires at least some unspecified minimal potency that is "potent enough." (Resp. at 19, 27, citing Tr. 334:12-15) The claim, however, is entirely unbounded as to the wide structural diversity of the claimed genus of compounds that may or may not satisfy these requirements, and is purposefully left open to all new compounds hereafter invented, as conceded by Dr. Bell. (Tr. 1301:1-3; 1323:11-14; 1323:22-1324:3) There is no legally adequate written description or enabling disclosure of the claimed

subset of PDE V inhibitors in the specification for the simple reason that UroPep had not made, did not possess, and, therefore, could not describe or enable, the claimed invention at the time it filed its application.

In fact, there is no suggestion in the four corners of the patent specification that just "selective" inhibition of PDE V, as opposed to PDE I and/or IV, is the key to treating BPH, as opposed to any other disclosed condition. No specific molecule within the scope of the claim is described as a suitably selective inhibitor of PDE V as opposed to undifferentiated selective inhibitors of "PDE I, IV, and V." No actual effective treatment of BPH with any claimed compound is described. No minimum level of potency is identified to ensure effective treatment. No actual effective dose for any claimed inhibitor is described. At the time of patent filing, the four corners of the patent prove that UroPep was speculating about which inhibitors of three different enzymes (PDE I, IV and V) might be effective in treating a myriad of prostatic conditions.

II. THERE IS NO ADEQUATE WRITTEN DESCRIPTION

A. Selective PDE V Inhibitors that Effectively Treat BPH In the Claimed Method Are Not Adequately Described

UroPep contends that Lilly argues that "UroPep needed to describe, and enable the synthesis, of every conceivable PDE5 inhibitor" (Resp. at 1)—but that is not Lilly's argument. Rather, relying on Federal Circuit authority, Lilly asserts that claims functionally describing a genus of compounds—including method claims that recite the use of such a functional genus for a therapeutic treatment—must be supported by a disclosure within the "four corners" of the specification that either (1) identifies a sufficient number of representative species to be used in the claimed method or (2) provides a structure-function correlation such that one skilled in the art can envision the genus of compounds to be used in the claimed method. (JMOL at 9-10, 11-12, 15) Whether the claim is to a compound or a method of treatment is of no moment here. *Univ. of*

Rochester v. G.D. Searle & Co., 358 F.3d 916, 926 (Fed. Cir. 2004) (whether a compound claim or method claim is "a semantic distinction without a difference" for purposes of the written description requirement); *see also Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1354 (Fed. Cir. 2010) (en banc). Neither criterion is satisfied here for reasons noted in Lilly's opening brief. (JMOL at 15-25)

An objective inquiry into the four corners of the patent demonstrates that its specification:

- Fails to provide sufficient representative compounds that are selective for PDE V **and** will effectively treat or prevent BPH;
- Fails to provide a relationship between a compound's structure and the required functional properties to selectively inhibit PDE V and effectively treat or prevent BPH;
- Fails to describe how to make predictable changes to the disclosed compounds to arrive at compounds within the scope of the claim with the required functional properties;
- Fails to differentiate among inhibiting PDE I, PDE IV, and PDE V, or among inhibiting those three enzymes for the treatment of a laundry list of prostate diseases;
- Fails to identify any of the 10 disclosed compounds as a selective inhibitor of PDE V or explain why 8 of the 10 disclosed compounds are excluded from the claim;
- Fails to provide any data showing any compound is effective in treating or preventing BPH;
- Fails to describe or differentiate what would be an "effective amount" among inhibitors of PDE I, IV and V;
- Fails to provide any guidance as to the level of potency needed for a PDE V inhibitor to be effective in treating or preventing BPH;
- Fails to describe how to assess effective treatment or prophylaxis of BPH; and

- Fails to describe tadalafil (the only PDE V inhibitor approved to treat BPH) or the chemical class from which tadalafil is derived or how any disclosed compound could be modified to obtain a compound structurally similar to tadalafil.

As Dr. Terrett testified, it is "impossible to say" whether all PDE V inhibitors would work to treat BPH. (Tr. 710:1-3) Thus, the only way to know whether a PDE V inhibitor compound is sufficiently "selective," "potent enough," and "effective" would be to test it. That is antithetical to the written description requirement, which ensures that inventors have actually invented what they claim, and have not merely described a problem to be solved by others while claiming all solutions to it. *Ariad*, 598 F.3d at 1353, 1356 ("[A] vague functional description and an invitation for further research does not constitute written disclosure of a specific inhibitor."); *Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed. Cir. 1993) ("Claiming all DNA[s] that achieve a result without defining what means will do so is not in compliance with the description requirement; it is an attempt to preempt the future before it has arrived.").

UroPep's reliance on its disclosure of sildenafil (e.g., Resp. at 13, 30) also is unavailing. Sildenafil is **excluded** by the express language of the claim and thus cannot provide the requisite exemplary support for molecules that are **not** excluded. The only compound actually claimed in the '124 patent is zaprinast.[1] But, based on the cited Truss paper, zaprinast does **not** meet the Court's requirement that it be 20 times more selective for PDE V compared to PDE I-IV. The

[1] UroPep also relies on MY5445, but nothing in the specification describes MY5445 as a selective inhibitor of PDE V as construed by the Court. Indeed, other than showing its chemical structure, the patent says nothing else about that compound. Thus, UroPep resorts to an uncited prior art paper to try to prove MY5445 is a selective inhibitor of PDE V. However, in that paper (PX 242), the reported data shows that MY5445 would sometimes be at least 20 times selective to PDE V compared to PDE I-IV, but, given the reported standard error, would sometimes be less than 20 times selective. (PX 242, Table III, at 3766) And, MY5445 is four times **less** potent than zaprinast (comparing IC50 for PDE V of 1.8 μM for MY5445 to IC50 for PDE V of .45 μM). The development of zaprinast was terminated in part because it was not potent enough. (PX 239 at 825)

specification also does not (1) provide what would be an effective amount of zaprinast to treat BPH, or (2) contain examples, either actual or prophetic, of using zaprinast to treat BPH. And zaprinast was never approved for any disease, has never been tested for treatment of BPH, and could not be determined to be effective for BPH without testing. (Tr. 338:6-339:9)

Nor does the specification describe any common structure that allows reasonable identification of such inhibitors. There is no common structure among the four compounds identified by UroPep (sildenafil, E4021, zaprinast, and MY5445). The so-called "frog" structure is nowhere identified in the patent as a common structural element in "selective" and "effective" PDE V inhibitors suitable for use in the claimed invention. It is clear on the face of the patent that the "frog" is found only in E4021, a compound explicitly excluded from claim 1; the other three compounds cited by UroPep do not have a "frog" structure. And the trial record showed that the "frog" also is found in PDE **IV** inhibitors, which plainly are excluded from the claim. (JMOL at 23) Contrary to UroPep's contention, Lilly was not required to object to this testimony to later point out that it is directly contradicted by the four corners of the patent text. Nor does the record support UroPep's simplistic description of the binding interaction between PDE V and its inhibitors as a description of a common inhibitor structure. (*See* JMOL at 20) Even if accepted as a description of how enzymes and inhibitors interact, which it is not, it says nothing about what structural elements in any given compound (much less the claimed genus of compounds) will cause such an interaction to occur either potently or selectively.

B. Ariad Controls the Outcome of this Case

The legal consequence of a deficient specification like that at issue here has already been decided by the en banc Federal Circuit in *Ariad* and its progeny. (JMOL at 11-12, 25) Contrary to UroPep's assertions (Resp. At 17-18), the facts of *Ariad* are directly applicable here. In *Ariad*, the Court acknowledged that the patent did, in fact, describe several different useable NF-kB inhibitor

molecules: "Like the other two classes of molecules, decoy molecules are presented hypothetically, but **unlike the other two classes of molecules, the specification proposes example structures for decoy molecules**." 598 F.3d at 1357 (emphasis added). Nevertheless, the description of a couple of decoy molecules in *Ariad* was insufficient: "Whatever thin thread of support a jury might find in the decoy-molecule hypothetical **simply cannot bear the weight of the vast scope of these generic claims**." *Id*. at 1358 (emphasis added). Thus, it is legally immaterial whether zaprinast, or MY5445, are 20-fold more selective for PDE V and effectively treat BPH (there is no evidence they do). The identification of one or two molecules will **not** provide a legally adequate written description for the "vast scope" of an undescribed genus of molecules that intentionally includes new molecules structurally unrelated to the described molecules.

C. The Field Was Neither "Mature" Nor "Predictable"

UroPep asserts the "field" was "mature" and "predictable," characterizing its claimed invention as the use of a "well known class of compounds in a mature field." (E.g., Resp. at 17, 18, 24, 32, 34, 36) This argument, however, is simply a thinly-veiled, improper attempt to substitute a naked allegation that those skilled in the art could cobble together the claimed invention based on the prior art for the required "four corners" disclosure. An adequate written description cannot be predicated on that which is undescribed but allegedly obvious from the art. *See Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1571-72 (Fed. Cir. 1997) ("One shows that one is 'in possession' of *the invention* by describing *the invention*, with all its claimed limitations, not that which makes it obvious." (citing *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991) (emphasis in original)); *see also Ariad*, 598 F.3d at 1352. Thus, the written description inquiry looks to the "four corners of the specification" to discern the extent to which the inventors had possession of the invention as broadly claimed. *Riviera v. Int'l Trade*

Comm'n, 857 F.3d 1315, 1322 (Fed. Cir. 2017) (citing *Ariad*, 598 F.3d at 1351 and *Lockwood*, 107 F.3d at 1571).

UroPep's allegation that "hundreds" of compounds were known in 1997 to be able to inhibit PDE V is irrelevant to whether the **claimed invention** is adequately supported by the specification. The claim requires PDE V inhibitors that are: (1) not one of the excluded compounds; (2) "selective"; and (3) "potent enough" (according to UroPep) to be "effective" to treat BPH. None of the alleged "hundreds" of compounds in the prior art were shown to actually satisfy these limitations. For example, most of the compounds disclosed in the Sybertz paper (DX 1377) lack information about their selectivity for PDE V compared to PDE I-IV. Moreover, UroPep's '061 patent (PX 193) expressly claims most of the compounds disclosed in the '124 patent as "selective inhibitors of PDE IV and/or PDE V"—which demonstrates that at least some of these compounds selectively inhibit PDE IV, and which plainly precludes their ability to selectively inhibit PDE V under the Court's claim construction.[2]

In this regard, this case is distinguishable from cases like *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1363 (Fed. Cir. 2006), where the question was merely whether the known poxvirus genome needed to be described. The analogous question here would be if the '124 patent merely mentioned "zaprinast" without disclosing its known chemical structure. In stark contrast, as mentioned above, the claims of the '124 patent recite limitations that may or may not be possessed

[2] Here, the lack of legally sufficient support for the negative limitation of claim 1 excluding 8 of the 10 disclosed compounds is pronounced. Respectfully, the explanation cannot be "double patenting." As noted, the excluded compounds include nearly all the compounds that are claimed as "selective inhibitors of PDE IV and/or PDE V" in the '061 patent. The compounds cannot be both selective PDE IV and PDE V inhibitors, and at least some of them must be selective PDE IV inhibitors. Excluding PDE IV inhibitors from a claim directed to PDE V inhibitors is not a double patenting issue. Moreover, as pointed out in Lilly's opening brief, zaprinast is claimed in both the '061 and '124 patents; as such, the exclusion of the compounds for "double patenting" purposes does not explain zaprinast.

by the prior art compounds. Further, in UroPep's own words, the compounds claimed in the '124 patent are those that are "potent enough" (Resp. at 19, 27), but the patent provides no guidance as to what "potent enough" is. In fact, Dr. Bell admitted that not all PDE V inhibitors are potent enough to be given in an effective amount to treat BPH and that the '124 patent does not define the minimum potency to be an effective amount. (Tr. 334:9-22)

The prior art actually belies UroPep's "predictability" contentions. Unrebutted testimony by Dr. Roehrborn—a urologist who has researched and treated BPH since 1984—established that in 1997 and still today BPH is a "complex," "poorly defined" and "highly variable" disease that is "complicated" and difficult to treat. (Tr. 526:11-527:4) Further, a 1993 paper (PX 242) stated "there is little information" on the structure-activity relationships of cGMP-specific inhibitors (including PDE V inhibitors) "because even the most potent inhibitors have very diverse molecular structures, making identification of the most important sites of interaction difficult." (PX 242 at 3765) That same paper also stated that "little is known about the *in vivo* actions and clinical effects of selective PDE V inhibitors." (*Id.*) As of 1997, only two PDE V inhibitors—zaprinast and sildenafil—had been clinically evaluated, and those results also contradict UroPep's "predictability" assertions. Sildenafil was clinically studied for **erectile dysfunction**, not BPH, and, more importantly, is a compound explicitly **excluded** from the scope of the claim. Zaprinast was only studied for asthma, but was determined to "not have adequate potency or selectivity to allow detailed exploration of the physiological or pharmacological effects of selective inhibition of type V PDE and the potential therapeutic indications." (PX 239 at 825) Therefore, the clinical evaluation of zaprinast had been abandoned **before** the filing date of the '124 patent. (DX 1377 at 385) Moreover, Drs. Bell and Terrett reported that zaprinast was only 4.7 times more selective for PDE V compared to PDE I (PX 183 at 1820), which clearly does not fall within the scope of the

Court's construction. And Dr. Bell admitted that he did not know if zaprinast would be effective in treating BPH even when administered at the clinically studied dosage. (Tr. 338:15-339:9)

The condemnation of zaprinast by UroPep's experts and others in the prior art as insufficiently potent and selective for PDE V to allow study of its therapeutic effects directly contradicts UroPep's contention that its suitability for use in this invention would have been well known to persons of skill in the art. Such contradiction indicates UroPep was not actually in possession of the invention now claimed. *See Boston Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1366 (Fed. Cir. 2011) (stating that "when the four corners of the specification directly contradict information that the patentee alleges is 'well-known' to a person of skill at the effective filing date, no reasonable jury could conclude that the patentee possessed the invention.") In *Boston Scientific*, the Federal Circuit specifically distinguished *Falko–Gunter Falkner* on this basis, and this distinction applies here as well. *Id*.

The patent disclosure is at best a legally insufficient research plan or an invitation to experiment in the field of pharmaceutical chemistry and drug development, which decided cases have long recognized is highly unpredictable. *See Rochester*, 358 F.3d at 925; *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1533 (Fed. Cir. 1987); *In re Fisher*, 427 F.2d 833, 839 (C.C.P.A. 1970); 2 Chisum on Patents § 5.04. This cannot be negated by Dr. Bell's naked, conclusory expert opinion that the field was "predictable." Under controlling Fifth Circuit law, an expert's opinion must be supported to provide substantial evidence on JMOL review. *Guile v. United States*, 422 F.3d 221, 227 (5th Cir. 2005). Thus, the court must "look to the basis of the expert's opinion, and not the bare opinion alone." *Id.* (quoting *Archer v. Warren*, 118 S.W.3d 779, 782 (Tex. App. 2003)). Dr. Bell's "bare opinion" about "predictability" and a "mature" field contradict the art, e.g., PX242, and is without support.

D. The Specification Also Does Not Support A Claim To Using Only PDE V Inhibitors To Treat Only BPH

As made clear by binding precedent, later added claims to a particular species within the scope of a genus (described in an earlier filed specification) are not adequately supported unless the specification provides specific "blaze marks" that would lead one skilled in the art to that particular species. The patent specification describes the possibility that inhibiting three different enzymes could be effective treating a variety of conditions affecting the bladder, penis, and prostate (col. 2:17-27), but nothing identifies PDE V inhibitors specifically as having any "special interest" as opposed to inhibitors of PDE I or PDE IV, whether for BPH or any of the other eight target conditions. Thus, the disclosure of the '124 patent is analogous to those that the Federal Circuit has repeatedly found insufficient. *See, e.g.*, *Boston Scientific*, 647 F.3d at 1367-69; *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571 (Fed. Cir. 1996); *In re Ruschig*, 379 F.2d 990, 994-95 (C.C.P.A. 1967) (application's undifferentiated description was deficient because it failed to provide sufficient "blaze marks" to guide a reader through the forest of disclosed possibilities).

UroPep fails to distinguish these cases in any meaningful way. UroPep's assertion that none of them applied to method claims is wrong. *Boston Scientific* specifically addressed method of treatment claims; and, in any event, whether a compound claim or a method claim is immaterial to the written description requirement. *Rochester*, 358 F.3d at 926. UroPep also argues that *Ruschig* is inapplicable because the genus there (half a million compounds) was much larger than that at issue here. Not so. On appeal, the applicants in *Ruschig* pointed out that, in addition to the half million compounds described in the specification, there was also a claim in the original specification that only disclosed 48 compounds, one of which was the compound chlorpropamide later recited in a rejected claim. 379 F.2d at 994. This, according to the applicants, was sufficient to guide one skilled in the art to chlorpropamide. *Id*. The Court rejected this argument, explaining

that to claim a sub-species of the genus, "something more than the disclosure of **a class of 1000, or 100, or even 48, compounds is required**." *Id.* (emphasis added). Here, there is an unknowable number (likely billions) of candidates within the genus of inhibitors of "PDE I, PDE IV, and PDE V"—and yet the claim recites only selective PDE V inhibition without any indication in the specification why this is the case, or why selective PDE V inhibition is of particular importance for BPH as opposed to the other diseases discussed in the specification.

UroPep contends its position is supported by *Snitzer v. Etzel*, 465 F.2d 899, 902-03 (C.C.P.A. 1972) and *In re Driscoll*, 562 F.2d 1245, 1250 (C.C.P.A. 1977). But these cases were specifically considered and, for the same reasons here, found inapposite in *Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1346 (Fed. Cir. 2013), because the broad specification at issue there "nowhere describes the actual functioning, thermostable alpha-amylase" recited in the later added claim to the sub-genus. Here, as discussed above, the specification also does not describe any particular PDE V inhibitor as 20 times more selective for PDE V than for PDE I-IV (as required by the Court's claim construction), and does not describe actually using any such selective PDE V inhibitors to effectively treat BPH specifically. As in *Novozymes*, one searches the '124 patent "in vain for the disclosure of even a single species that falls within the claims or for any 'blaze marks' that would lead an ordinarily skilled investigator toward such a species among a slew of competing possibilities." *Id*. at 1349.

UroPep further asserts that "[t]he '124 patent specification repeatedly refers to using inhibitors of PDE 1, 4 *or* 5." (Resp. at 7 (UroPep's emphasis)) However, the two instances cited by UroPep do not establish the primacy of PDE V compared to PDE I or PDE IV. On the contrary, the patent more frequently cites to "inhibitors of PDE I, IV **and** V" (*see* '124 pat., col. 2:6-8, 17-19, 26, 28; col. 7:32-34) (emphasis added)—and **never** in the context of treating just BPH.

Moreover, the only examples in the patent use sildenafil, which is excluded from the claims, and are not used (actually or prophetically) for the treatment of any disease, let alone just BPH. UroPep also wrongly asserts that "the specification identifies BPH as a particularly relevant disease to be treated with these inhibitors." (Resp. at 7, citing the '124 patent at col. 2:17-20). However, the quoted language relied on by UroPep is incomplete. The complete paragraph, spanning lines 7-17 of column 2 of the patent, does not call out BPH only but merely lists BPH among several other conditions that may be treated by inhibitors of PDE I, IV and V.

Left without a compelling response on the merits, UroPep argues that Lilly waived this argument. That contention is without merit. Lilly gave notice that it contested the '124 patent's compliance with the statutory written description requirement applicable in *Novozymes*, *Ariad*, and all the other written description cases. Indicating it was "familiar with the issues," the Court told Lilly's counsel to make its Rule 50(a) invalidity arguments "in bite-size form." (Tr. at 1392:16-1393:1) Following this instruction, Lilly's counsel stated its Rule 50(a) motion by reference to the well-established statement of what is required to satisfy written description. (Tr. at 1393:11-14) The Court denied the motions without further discussion and consistent with the its statements that any Rule 50(a) motions will become Rule 50(b) motions, at which point in time, the aggrieved party "will get an opportunity for much more comprehensive briefing than [the party] would be able to do right now. So, let's save ourselves some writing." (Tr. 1244:10-16)

Fifth Circuit law, which governs UroPep's waiver argument, liberally construes Rule 50(a). *See Blackboard, Inc. v. Desire2Learn, Inc.*, 574 F.3d 1371, 1380 (Fed. Cir. 2009) (applying Fifth Circuit law to hold that the defendant's Rule 50(a) motions, even though cursory, were more than sufficient in the context of the motions to serve the purposes of Rule 50(a)) (citing *Navigant Consulting, Inc. v. Wilkinson*, 508 F.3d 277, 288-89 (5th Cir. 2007). The four corners of the '124

patent (clearly the most critical document in evidence) does not differentiate between inhibiting PDE I, IV and V for any of the laundry list of conditions affecting the prostate, bladder, and penis. Lilly also presented witness testimony demonstrating not only the written description problems with the breadth of the claimed genus of selective PDE V inhibitors to treat BPH, but also with the undisputed fact that the specification does not distinguish inhibition of PDE I, IV and V to treat any of nine different conditions or identify which of the disclosed compounds inhibit which PDE.[3] Under controlling Fifth Circuit law and these circumstances, Lilly's Rule 50(a) motion was more than sufficient under to preserve its invalidity arguments.

III. THE '124 PATENT FAILS TO COMPLY WITH THE ENABLEMENT REQUIREMENT AS A MATTER OF LAW

UroPep's assertion that Lilly ignores the *Wands* factors is without merit. Lilly discussed those factors in the context of *Wyeth and Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380 (Fed. Cir. 2013). *Wyeth* addressed the *Wands* factors important here—specifically, the breadth of the claims, guidance provided by the specification, the unpredictability of the chemical arts, the complexity of the invention, and the limited knowledge of the condition being treated (*id.* at 1384)—and found the specification inadequate for reasons that apply with equal force here.

Contrary to UroPep's assertions, the alleged factual differences between this case and *Wyeth* actually support Lilly's assertions that the '124 patent is invalid. For example, in *Wyeth*, the patent claim as construed provided some structure, i.e., the known compound sirolimus. *Id.* at 1385

[3] *See* Tr. 1306:21-1307:8 (Dr. Bell testifying that the patent does not identify which of the disclosed compounds inhibit PDE I, IV or V); Tr. 710:4-711:1 (Dr. Terrett testifying that not all of the compounds in the disclosed class of quinazolines would inhibit PDE I, IV, or V, or any PDE); Tr. 657:11-15 (Dr. Uckert testifying that he did not know why the disclosed compounds were included in the patent); Tr. 528:23-530:11 (Dr. Roerhborn testifying that there is no disclosure of any particular inhibitor of PDE I, IV or V disclosed as being used in the organ bath test described in the patent); Tr. 185:4-8 (Dr. Uckert testifying that he has never treated a patient with BPH or conducted any test in which a PDE V inhibitor was given to a man with BPH).

(stating the invention was "a new method of use of a known compound (sirolimus) *and* any other compounds that meet the construction's structural and functional requirements" (emphasis in original)). In addition, the Court accepted that the rapamycin analogs should have molecular weights below 1,200 Daltons to be permeable across cell membranes. *Id.* at 1384-85.

In contrast, here, claim 1, as construed by the Court, contains no structure or any molecular weight limitation, but is purely functional. The only limitation is that the compound be "selective," not be one of the eight excluded compounds and, according to UroPep, "potent enough" to be effective to treat BPH. But there is no "guidance" in the '124 patent's disclosure that helps identify "selective" and "potent enough" compounds to be given in "effective amounts" to treat BPH. Moreover, the references to the Truss paper and two other papers in the patent are entirely unhelpful in identifying "selective" PDE V inhibitors. In fact, a person of skill in the art relying on the Truss paper (DX 1390) would be led down the path of concluding that zaprinast, specifically claimed as suitably selective in dependent claim 2, was **not** a selective PDE V inhibitor and, therefore, **not** suitable for use in the invention. (Tr. 689:17-690:17) The other two papers cited in the patent (Nicholson and Galvan) are of no help because neither tested for PDE V inhibition.[4] (Tr. 691:2-18) The actual disclosure of the '124 patent was effectively abandoned by UroPep during trial. Instead UroPep, through Dr. Bell, now primarily relies on undisclosed methodologies used by Pfizer or the "Eisai company." (Resp. at 40) That is not a sufficient enabling disclosure.

[4] UroPep argues that Lilly waived the right to raise any challenge to the enablement of the selectivity requirement because it did not raise it in its Rule 50(a) motion. That contention lacks merit for the same reasons that the parallel contention regarding written description fails. In light of the Fifth Circuit's liberal view of Rule 50(a) motions, the Court's direction to keep the motions "bite-size," and the fact that both the Court and UroPep were apprised of the import of Dr. Beavo's testimony (especially given the previous indefiniteness summary judgment briefing), the issue was adequately preserved.

Further, "selectivity" is only one required property of the claimed compounds; efficacy in treating BPH is also required, and nothing in the '124 patent describes any of the properties necessary to determine how a claimed drug compound will work in a person's body. (*See* JMOL at 30-35) Given the uncontroverted testimony of Dr. Terrett that it would be "impossible to say" whether all PDE V inhibitors could effectively treat BPH, and Dr. Bell's testimony that only selective PDE V inhibitors that are "potent enough" are within the claim scope, there is no question that an iterative, trial-and-error process of screening and testing a large number of compounds would be required. While the exact number of candidate PDE V inhibitors is unknowable, Dr. Bell acknowledged that there are at least "tens of thousands" of PDE V inhibitors known today. (Tr. 341:23-342:1) And Dr. Bell conceded that what the '124 patent really claims a "method of enabling the discovery of new drugs," thus covering not only compounds known in 1997 but also "brand-new" compounds. (Tr. 1323:11-14; 1323:22-1324:3)

UroPep's attempt to excuse the manifest deficiencies in the patent's disclosure by characterizing the field of its alleged invention as "predictable" or the experimentation "routine" fails for precisely the same reason it fails to rehabilitate UroPep's inadequate written description. *See Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997) ("It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute an adequate enablement."). Further, *Wyeth* would still dictate the outcome here even accepting Dr. Bell's bare opinion that the experimentation to identify selective and effective PDE V inhibitors is "routine." In *Wyeth*, the Court accepted as true that one of ordinary skill could **routinely** use the assays disclosed in the specification to determine desired functional effects in candidate compounds—but still found the experimentation was undue and the patent invalid. 720 F.3d at 1385-86. Here, as in *Wyeth*, the experimentation to identify "selective"

and "potent enough" PDE V inhibitors among at least "tens of thousands of compounds" to determine which ones can effectively treat BPH—even if accepted to be routine—is undue.

And finally, just as in *Wyeth*, the '124 patent's specification discloses only a starting point with, at most, two weakly potent and poorly selective compounds potentially within the scope of the claim, along with a selectivity assay that does not work, that would require further iterative research in the field of treating BPH—a disease that is indisputably "complex," "poorly defined," "highly variable," and "complicated." (Tr. 526:11-527:4) Even putting aside the challenges of synthesizing and identifying potential selective PDE V compounds that are "potent enough" to effectively treat BPH, the '124 patent offers no guidance about particular substitutions, modifications, or other classes of compounds that might selectively inhibit PDE V, be potent enough, and effectively treat a disease as complex and variable as BPH. In sum, the '124 patent's disclosure is legally inadequate to enable practice of this alleged invention as broadly as it is claimed. *Wyeth*, 720 F.3d at 1386; *see also ALZA Corp. v. Andrx Pharms., LLC*, 603 F.3d 935, 942 (Fed. Cir. 2010) (patent is not enabled where the specification provides "only a starting point, a direction for further research" (quoting *Auto. Tech. Int'l, Inc. v. BMW of N. Am., Inc.*, 501 F.3d 1274, 128) (Fed. Cir. 2007))); *Genentech*, 108 F.3d at 1366 ("Tossing out the mere germ of an idea does not constitute enabling disclosure.").

IV. UROPEP'S ARGUMENTS PROVE THE CLAIM IS INDEFINITE

Effectively conceding that the Truss paper's protocol is unworkable, UroPep now contends that it was merely "signposting" the use of "similar" fractionation methods (Resp. at 42). Having cast aside Truss's protocol, UroPep then pays lip service (as does the patent) to Galvan and Nicholson as stand-ins for Truss; however, neither of those papers' protocols even test for PDE V inhibition. UroPep thus argues that determining PDE V selectivity could be reliably accomplished "under the right conditions" using methods that are "very common" and "commonly used through

the industry"—such as the methods used by Pfizer. (*Id.*) But that is the very point: even "commonly used" methods give variable results depending on the conditions (such as the tissue tested, enzyme concentration, laboratory procedures, and other experimental variables); in other words, determining the "right conditions" is critical. (Dkt. 173, Lilly summary judgment motion on indefiniteness, at pp. 3-9) Moreover, neither Pfizer's methods nor any other "commonly used" methods are disclosed in the patent. Consequently, the determination of selectivity is based on tests that are either unworkable, not relevant to PDE V, or not disclosed. Without specifying the method or the "right conditions," there is no way to determine whether a compound is within the scope of the claim or not. (*Id.* at pp. 12-17, and cases cited therein)

V. THE ASSERTED CLAIMS ARE EITHER ANTICIPATED OR INADEQUATELY DESCRIBED AND ENABLED

In its recent order denying UroPep's motion for attorney fees, the Court found:

> Lilly is correct that the herb epimedii, or Horny Goat Weed, contains icariin, which is a selective PDE5 inhibitor. It is also true that the Cheung reference recommends the ingestion of Horny Goat Weed to treat BPH, and that the Cheung reference antedates the priority date of the '124 patent. Cheung reports that in a clinical study of 34 patients, the herbal treatment of what Cheung calls "prostate hypertrophy," i.e., BPH, produced positive results in 32 patients—more than 90 percent of the patients tested. Moreover, Lilly's expert, Dr. Claus Roehrborn, interpreted the pertinent passage of the Cheung reference to mean that "34 patients were given the PDE5 inhibitor contained in herba epimedii, and it was found to have been an effective amount by their response." Dkt. No. 342, Trial Tr. 559.

(Dkt. 389 at 6) The Court further noted that "the gap in the proof was over whether those patients who received Horny Goat Weed were among the patients who showed improvement following their treatment." (*Id.* at 7) Respectfully, the reported success for 32 of 34 patients satisfies the clear and convincing standard that at least some improved patients received icariin. Even if such a gap existed, it is not relevant to the legal test of anticipation. As a matter of law, there is no requirement that Cheung demonstrate utility or, for that matter, commercial viability, FDA approval, use or

recognition by medical doctors, associations, or groups. As noted in *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1326 (Fed. Cir. 2005), a case remarkably similar to this one, "a prior art reference need not demonstrate utility in order to serve as an anticipating reference under section 102." To anticipate the claimed method, Cheung need only instruct the administration of an effective amount of a selective PDE5 inhibitor to treat BPH. Whether the amount that was given is actually effective is not relevant; nor is it relevant whether an effective amount was actually given, so long as the instruction to practice the claimed method is there. *Id.* (neither proof of efficacy nor actual performance is required in order for a reference to be enabled for purposes of anticipation) (citing *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1376, 1379 (Fed. Cir. 2001).

During trial and JMOL briefing, there were dueling submissions on whether the amount of icariin disclosed in Cheung should be compared to tadalafil (which is nowhere disclosed in the patent and is the current gold-standard of treatment) or to zaprinast (which is disclosed, expressly claimed, and relied on by UroPep to rebut Lilly's arguments). Cheung need not disclose a FDA-approvable, commercially-viable, or as-good-as-tadalafil use to be anticipatory. In any event, icariin's potency falls between zaprinast and MY5445, the only two compounds cited by UroPep as selective, potent enough inhibitors not excluded by the claim. (*See* PX 242, comparing IC50 of MY5445 for PDE V of 1.8 μM to IC50 of zaprinast for PDE V of .45 μM; *and see* DX 1328 at 1352, Table I, showing icariin's IC50 for PDE V ranging from .75 to 1.1 μM). If both zaprinast and MY5445 are "potent enough" to be given in effective amounts to treat BPH, so is icariin.

Finally, Cheung provides greater detail regarding effective treatment of BPH than in the '124 patent. If Cheung's disclosure is insufficient to anticipate, it inevitably follows that the less specific disclosure in the patent is likewise a legally inadequate written description and enabling

disclosure of "effective" amounts. *Constant v. Advanced Micro Devices, Inc.*, 848 F.2d 1560, 1569 (Fed. Cir.), *cert. denied*, 488 U.S. 892 (1988) ("The disclosure in [the prior art] is at least at the same level of technical detail as the disclosure in the . . . patent. If disclosure of a [claim limitation] is essential for an anticipating reference, then the disclosure in the . . . patent would fail to satisfy the enablement requirement of 35 U.S.C. § 112, First ¶.")

VI. IF ADEQUATELY DESCRIBED, ENABLED, AND NOT ANTICIPATED, THE CLAIMED INVENTION IS LEGALLY OBVIOUS

If the Court accepts as true that all "potent enough" PDE5 inhibitors would work to treat BPH, and **if** that is adequately described in the patent and any further experimentation would have been unnecessary, then the invention was predicated on the obvious: potent inhibitors of PDE V will relax smooth muscle, a mechanism already known to effectively treat BPH.

PharmaStem v. Therapeutics, Inc. v. ViaCell, Inc., 491 F.3d 1342 (Fed. Cir. 2007) is instructive. In that case, the claimed method of treatment was "based on the discovery that blood from a newborn infant's umbilical cord is a rich source of a type of stems cells useful for rebuilding an individual's blood and immune system after that system had been compromised by disease or a medical treatment such as chemotherapy." *Id.* at 1347. On appeal, the Federal Circuit reversed the district court's denial of JMOL for obviousness: "The evidence at trial demonstrated that the patentees did not invent a new procedure or a new composition; instead, they simply provided experimental proof that the cord blood could be used to effect hematopoietic reconstitution of mice and, by extrapolation, could be expected to work in humans as well." *Id*. at 1364-65.

Here, it was known that BPH could be treated by relaxing smooth muscle in the prostate and it was known that smooth muscle could be relaxed by inhibiting PDE5 that was functionally present in various parts of the body, including the urogenital tract. All the UroPep researchers discovered was that PDE5 was functionally present in another part of the body (the prostate, also

part of urogenital tract). Further taking as true UroPep's repeated assertions at trial and in its JMOL response, UroPep concedes a reasonable expectation that inhibition of PDE V in the prostate (once PDE V was found to be functionally present there) would be effective in treating BPH. *See id*. at 1360, 1364.

Similarly, if UroPep's contentions regarding written description and enablement are accepted, then the UroPep researchers did not invent a new procedure or new composition of PDE V inhibitors but simply alluded to experimental evidence that PDE V inhibitors are able to relax smooth muscle in prostate tissue *in vitro*. Even taking as true that the UroPep inventors proved PDE V was functionally present in the prostate, the conclusion that inhibition of PDE V will relax smooth muscle in the prostate and treat BPH was not inventive in nature. *Id.* at 1363. Given that the jury was legally required to believe that relaxation of smooth muscle was a known way to treat BPH and inhibition of PDE V relaxed smooth muscle, *see id.* at 1364, no reasonable jury could have found the claimed invention nonobvious.

VII. CONCLUSION

UroPep's remaining arguments in its response are rebutted in Lilly's opening brief. For the reasons there stated and further stated herein, the Court should enter judgment as a matter of law that asserted claim 1 of the '124 patent is invalid, or, in the alternative, grant a new trial.

Dated: July 27, 2017

BARNES & THORNBURG LLP

By: */s/Todd G. Vare*

Todd G. Vare
Jeff M. Barron
BARNES & THORNBURG LLP
11 South Meridian Street
Indianapolis, Indiana 46204
Telephone: (317) 231-7735
todd.vare@btlaw.com
jeff.barron@btlaw.com

Victor D. Vital
Jon B. Hyland
BARNES & THORNBURG LLP
2100 McKinney Avenue, Suite 1250
Dallas, Texas 75201
Telephone: (214) 258-4123
victor.vital@btlaw.com
jon.hyland@btlaw.com

Felicia J. Boyd (admitted *pro hac vice*)
Anthony H. Son
BARNES & THORNBURG LLP
225 South Sixth Street, Suite 2800
Minneapolis, Minnesota 55402
Telephone: (612) 333-2111
felicia.boyd@btlaw.com
ason@btlaw.com

Attorneys for Defendant
Eli Lilly and Company

CERTIFICATE OF SERVICE

The undersigned certifies that the foregoing document was filed electronically in compliance with Local Rule CV-5(a). As such, this document was served on all counsel who are deemed to have consented to electronic service. Local Rule CV-5(a)(3)(A). Pursuant to Fed. R. Civ. P. 5(d) and Local Rule CV-5(d) and (e), all other counsel of record not deemed to have consented to electronic service were served with a true and correct copy of the foregoing by email and/or fax, on this the 27th day of July, 2017.

/s/Todd G. Vare